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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,822	01/31/2006	Hidehito Kotani	BY0029YP	6147

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MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
09/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,822	KOTANI ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/26/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received on 7/8/09. Applicant's election without traverse of group 6, claims 8-11, drawn to methods for treating obesity by inhibiting fatty acid synthesis by administering to an individual an RNAi molecule is acknowledged, as is Applicant's election of the species of an siRNA molecule consisting of SEQ ID NOS: 9 and 10.

Claims 1-7 and 12-30 were canceled as requested.

Claims 8-11 remain pending and are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The elected invention is a method of treating obesity by inhibiting fatty acid synthesis in an individual comprising administering to the individual an siRNA consisting of SEQ ID NO: 9 and SEQ ID NO: 10 in an amount effective to lower Slc25a10 gene

expression in the individual, relative to the expression observed in the absence of the siRNA.

The invention as claimed and disclosed is considered to be inoperative for at least three reasons. First, SEQ ID NOS: 9 and 10 are DNA oligonucleotides, not RNA oligonucleotides, therefore they could not form an siRNA. Second, even if they were RNA oligonucleotides, they could not form an siRNA because they are not complementary to each other. Third, neither oligonucleotide is complementary to any sequence of substantial length in the intended target region, i.e. position 556 of a Slc25a10 mRNA deduced from the NM_012140 cDNA disclosed in the specification at page 31.

The sequences of SEQ ID NOS: 9 and 10 are shown below, with SEQ ID NO: 10 shown in both orientations.

```
SEQ ID NO: 10  5′-aagagggtctcaggagactgtcctgtctc-3′
SEQ ID NO: 9   5′-aaacagtctcctgagaccctccctgtctc-3′
SEQ ID NO: 10  3′-ctctgtcctgtcagaggactctgggagaa-5′
```

As indicated above, and evidenced by the Sequence Listing filed 1/31/06, SEQ ID NOS: 9 and 10 are DNA oligonucleotides, not RNA oligonucleotides, so there can be no such thing as an siRNA consisting of SEQ ID NOS: 9 and 10. It is also apparent from further inspection that SEQ ID NOS: 9 and 10 are not complementary, and would not hybridize to form an siRNA under physiological conditions even if they were composed of RNA. In fact, SEQ ID NOS: 9 and 10 are identical at positions 1, 2, 6, 9, 10, 14-17, 19, and 22-29, i.e. they are identical at 18 of 29 positions (62% identity). Because the sequences are not palindromic, this high degree of identity indicates a lack of complementarity. An attempt by the Office to align SEQ ID NOS: 9 and 10 as

complementary sequences using an alignment tool failed. If one attempts to align SEQ ID NOS: 9 and 10 as complements with 0-, 1-, or 2-nucleotide 3' overhangs, then the percent complementarity is about 24%, 31%, and 28%, respectively, which is close to the amount of complementarity expected for randomly selected sequences (25%).

The specification at pages 31 and 32 indicates that SEQ ID NO: 9 is a sense sequence, and SEQ ID NO: 10 is an antisense sequence. Together they are purported to form an siRNA directed against position 556 of the human Slc25a10 gene (NM_012140), which comprises instant SEQ ID NO: 2 (see page 31, line 14 to page 32, line 3). Nucleotides 521-580 of instant NM_012140 are shown below.

```
521 ggatggcctg taccgcgtag ctcgtgaaga gggtctcagg agactgttct cgggtgcaac 580
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The sequence of SEQ ID NO: 9 does not occur in this region. Neither does SEQ ID NO: 10, or its complement. Interestingly, the sequence of nucleotides 1-22, 24, and 25 of SEQ ID NO: 10 is present at sense nucleotides 556-577, 579, and 580 of SEQ ID NO: 2. So, the RNA version of SEQ ID NO: 10 would actually be better suited to function as a sense siRNA strand against Slc25a10 mRNA than as an antisense siRNA strand. However, SEQ ID NO: 9 shows no significant complementarity to nucleotides 177-198 of instant SEQ ID NO: 2, and would not be expected to function as antisense to this sequence.

The Office performed a BLAST search on SEQ ID NO: 9, and it was determined that it was 69% complementary to nucleotides 1063-1082 of GenBank Accession FLJ60124, i.e. nucleotides 2-21 SEQ ID NO: 9 are the antisense of nucleotides 1063-1082 of FLJ60124. FLJ60124 is a nuclear gene encoding Homo sapiens mitochondrial ribosomal protein L12 (MRPL12). An alignment was performed

between FLJ60124 and instant SEQ ID NO: 2, and no significant similarity was found. A blast search of SEQ ID NO: 10 showed it had 48% identity to nucleotides 275-303 of instant SEQ ID NO: 2. So, even if SEQ ID NOS: 9 and 10 could form an siRNA under physiological conditions, the preferred target of that siRNA would be FLJ60124 mRNA, because SEQ ID NO: 9 is far more complementary to FLJ60124 mRNA than SEQ ID NO: 10 is to Slc25a10 mRNA. Note that even though FLJ60124 encodes a mitochondrial protein, it is a nuclear gene and not a mitochondrial gene, so there is no question of performing RNAi on a mitochondrial mRNA.

Based on the foregoing, SEQ ID NOS: 9 and 10 appear to be unrelated, and RNA versions of these oligonucleotides would not be expected by one of skill in the art to form an siRNA targeted to position 556 of SEQ ID NO: 2, with SEQ ID NO: 10 functioning as an antisense, as is taught in the specification. Furthermore, neither SEQ ID NO: 9 nor 10 would reasonably be expected by those of skill in the art to be able to serve as an siRNA antisense strand that recognizes Slc25a10 mRNA derived from instant SEQ ID NO: 2, because these oligonucleotides are insufficiently complementary to the target mRNA. This is apparent because the prior art shows that the efficiency of siRNA function decreases with complementarity of antisense sequences to target mRNA, and in some cases a single mismatch has been sufficient to eliminate activity. See e.g. Tuschl et al (The siRNA user guide, 2003, page 2 second paragraph) or Holen et al (Nucl. Acids Res. 30(8): 1757-1766, 2002) at e.g. page 1763, left column, second paragraph).

It is noted that the specification as filed indicates at page 31 and Figs 6b and 7a that an siRNA consisting of SEQ ID NOS: 9 and 10, called 'H4', was used to inhibit expression of Slc25a10 in cultured cells by targeting nucleotide 556 of SEQ ID NO: 2. However, in view of the foregoing discussion, one of skill in the art would not believe that an siRNA recognizing Slc25a10 mRNA could be formed from these two oligonucleotides because 1) they are DNAs, not RNAs; 2) they are not complementary to each other; and 3) neither oligonucleotide is complementary to any sequence of substantial length in an mRNA that could be deduced from SEQ ID NO: 2. For these reasons, the invention as disclosed and claimed is considered to be inoperative, and therefore one of skill in the art would have to perform undue experimentation in attempting to use it.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official

central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer/
Primary Examiner, Art Unit 1635